What is claimed is:

1. A method of producing an activated ester of polyethylene glycol (PEG), comprising the step of activating PEG with N,N'-disuccinimidyl oxalate or 1,1'-bis[6-(trifluoromethyl)benzotriazolyl] oxalate under the appropriate conditions.

2. The method according to claim 1, comprising the step of activating PEG with N,N'-disuccinimidyl oxalate.

3. The method according to claim 2, wherein the ratio of N,N'-disuccinimidyl oxalate to PEG is 30 :1 or less.

4. The method of producing a N,N'-disuccinimidyl ester of polyethylene glycol (PEG) according to claim 2, wherein an organic base is used as a catalyst.

5. The method of producing a N,N'-disuccinimidyl ester of polyethylene glycol (PEG) according to claim 4, wherein the base catalyst is selected from the group consisting of pyridine and N,N'-4-dimethylaminopyridine.

6. A method of producing a PEG-nucleophile conjugate, comprising of reacting the PEG active ester of claim 2 with a biologically active nucleophile under appropriate conditions to form a PEG-nucleophile conjugate.

7. A method of producing a PEG-linker-nucleophile conjugate, comprising the steps :

   (a) reacting the PEG active ester of claim 2 with a linker; and

   (b) reacting the resulting PEG-linker with a biologically active nucleophile under appropriate conditions to form a PEG-linker-nucleophile conjugate.

8. The method according to claim 6 or 7 wherein said biologically active nucleophile is a peptide or a protein.

9. The method according to claim 8, wherein said PEG active ester is reacted with said peptide or protein in the molar ratio of between 1 and 30 moles active ester to 1 mol protein or with said

linker in the molar ratio of 1 mole active ester to 1 to 10 moles linker.

10. The method according to claim 7, wherein the PEG-linker(s) conjugate is activated with N,N'-disuccinimidyl oxalate, and subsequently reacted with a peptide or protein in the molar ratio of between 1 and 30 moles active ester to 1 mol peptide or protein to form PEG-linker(s) peptide or protein conjugate

11. The method according to claim 1, comprising the step of activating PEG with 1,1'-bis[6-(trifluoromethyl)benzotriazolyl] oxalate.

12. The method according to claim 11, wherein the ratio of 1,1'-bis[6-(trifluoromethyl)benzotriazolyl] oxalate to PEG is 30 :1 or less.

13. The method of producing a 1,1'-bis[6-(trifluoromethyl)benzotriazolyl] ester of polyethylene glycol (PEG) according to claim 11, wherein an organic base is used as a catalyst.

14. The method of producing a 1,1'-bis[6-(trifluoromethyl)benzotriazolyl] ester of polyethylene glycol (PEG) according to claim 13, wherein said base catalyst is selected from the group consisting of pyridine and N,N'-4-dimethylaminopyridine.

15. A method of producing a PEG-nucleophile conjugate, comprising of reacting the PEG active ester of claim 11 with a biologically active nucleophile under appropriate conditions to form a PEG-nucleophile conjugate.

16. A method of producing a PEG-linker-nucleophile conjugate, comprising the steps :

(a) reacting the PEG active ester of claim 11 with a linker; and

(b) reacting the resulting PEG-linker with a biologically active nucleophile under appropriate conditions.

17. The method according to claim 15 or 16 wherein said biologically active nucleophile is a peptide or a protein.

18. The method according to claim 17, wherein said PEG active ester is reacted with said peptide or protein in the molar ratio of

between 1 and 30 moles active ester to 1 mol protein or with said linker in the molar ratio of 1 mole active ester to 1 to 10 moles linker.

19. The method according to claim 16, wherein the PEG-linker(s) conjugate is activated with 1,1'-bis[6-(trifluoromethyl)benzo-triazolyl] oxalate, and subsequently reacted with a peptide or protein in the molar ratio of between 1 and 30 moles active ester to 1 mol peptide or protein to form PEG-linker(s) peptide or protein conjugate.

20. A PEG-nucleophile or PEG-linker-nucleophile conjugate prepared according to claim 6 or 7, wherein said nucleophile is an hGH antagonist or an anti TNF_α antibody.

21. A PEG-nucleophile or PEG-linker-nucleophile conjugate prepared according to claim 15 or 16, wherein said nucleophile is an anti TNF_α antibody or an hGH antagonist.

22. The conjugate of claim 21 wherein said TNF_α antibody is a CDR-grafted, hTNF40-based modified Fab.

23. A composition comprising of a PEG-nucleophile conjugate, with or without a linker, prepared according to claim 6, 7, 15, or 16.

24. A composition comprising of a PEG-nucleophile conjugate, with or without a linker, prepared according to claim 20.

25. A composition comprising of a PEG-nucleophile conjugate, with or without a linker, prepared according to claim 21.

26. A composition comprising of a PEG-nucleophile conjugate, with or without a linker, prepared according to claim 22.

27. A method of treating a patient in need thereof with a PEG-nucleophile conjugate, with or without a linker, according to claim 20.

28. A method of treating a patient in need thereof with a PEG-nucleophile conjugate, with or without a linker, according to claim 21.

29. A method of treating a patient in need thereof with a PEG-nucleophile conjugate, with or without a linker, according to claim 22.